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SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE

Department of Microbiology
and Immunology

SAN FRANCISCO, CALIFORNIA 94143

04 February 1980

Dr. David Baltimore
Institute of Cancer Research
Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Dear David:

Your seminar is scheduled for 4PM on the 25th of March under joint sponsorship of Microbiology and Biochemistry. I would anticipate a large audience well-versed in molecular biology but (with a few local exceptions) surprisingly ignorant about retroviruses.

We would like to arrange some social occasion for your visit. Can you anticipate how tired you are likely to be and what sort of evening you would most like? We are prepared for anything from a quiet evening with the family (actually rather difficult with our second son) to a glamorous night of SF highlife. Let us know.

Re: our phone conversation. I really don't see why linears cannot integrate directly. Since the DNA is initially unlinked to cell DNA, there is no need for an internal resolution sequence, as I read the Shapiro paper. In fact, the free ends of the linear facilitate the process, and I expect the formation of a noncovalent "cruciform" joint between the ends (by basepairing between inverted repeats on the same strand) is an intermediate in the process. Having an extra base or two at the ends of linear DNA not involved in the inverted repeat might make the ends still more accessable for insertion. I suspect the usual "two-copy" circle is a dead end from the integration standpoint. (We actually have some data on this issue, using religated cloned DNA to transfect mammalian cells; integration can occur at many sites within viral DNA.) To make the circle as an obligate intermediate would seem to be a mistake, since that would only require that the cell provide a site-specific cleavage to regenerate the convenient ends the DNA originally had. Your point about the gyrase is amusing (it is mentioned in the Shapiro paper but I paid inadequate attention to it before); one can make some titillating testable predictions about subsequent replication of viral or flanking DNA based upon the polarity of the cutting of the cell sequence.

I look forward to discussing these issues with you. In the meantime, you and others in your lab might enjoy discussing them with John Majors. He has done absolutely all the work on the MMTV proviruses and is now in the Manly-Sharp-Gefter axis looking for steroid-mediated transcription in vitro of his cloned steroidally-responsive provirus. I'm sure he would be happy to talk informally to your group. (He is, incidentally, one of the best people we've ever had here

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and will soon be looking for a job; we would appreciate any ideas you might have. He is extremely modest but I am certain you will not be deceived by that.)

With best wishes to you and Alice,

Harold E. Varmus, M.D.
Professor of Microbiology and
Immunology.

P.S. I will be sending the Cold Spring Harbor drafts next week. We can argue later about nomenclature. I am willing to give up "3' R 5'" but I don't like LTR much either.

HEV:jm